Thrombotic Microangiopathy

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Agenda

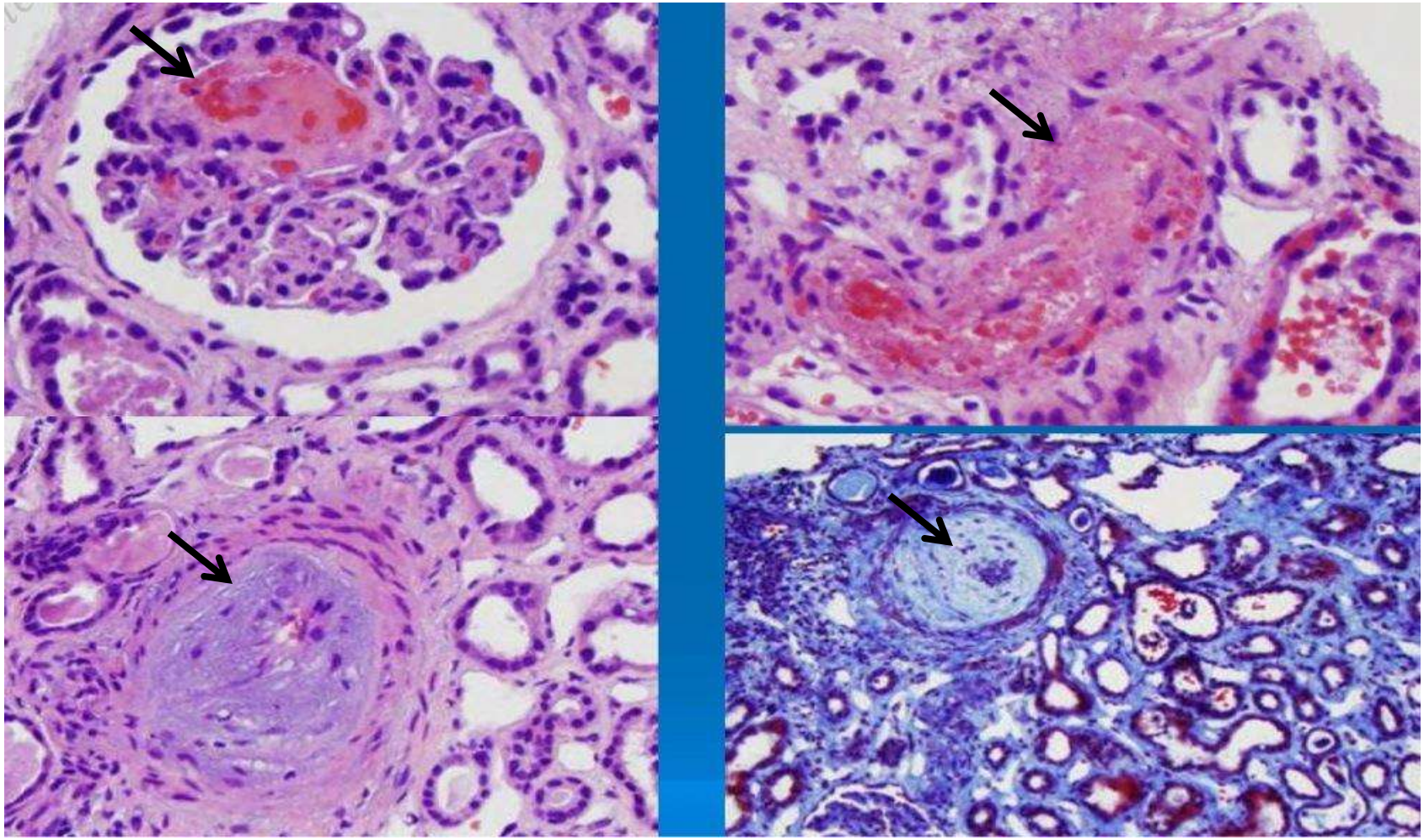
- Spectrum of TMA
- TTP
- HUS
- Transplant associated TMA
- Therapy

Definition of TMA

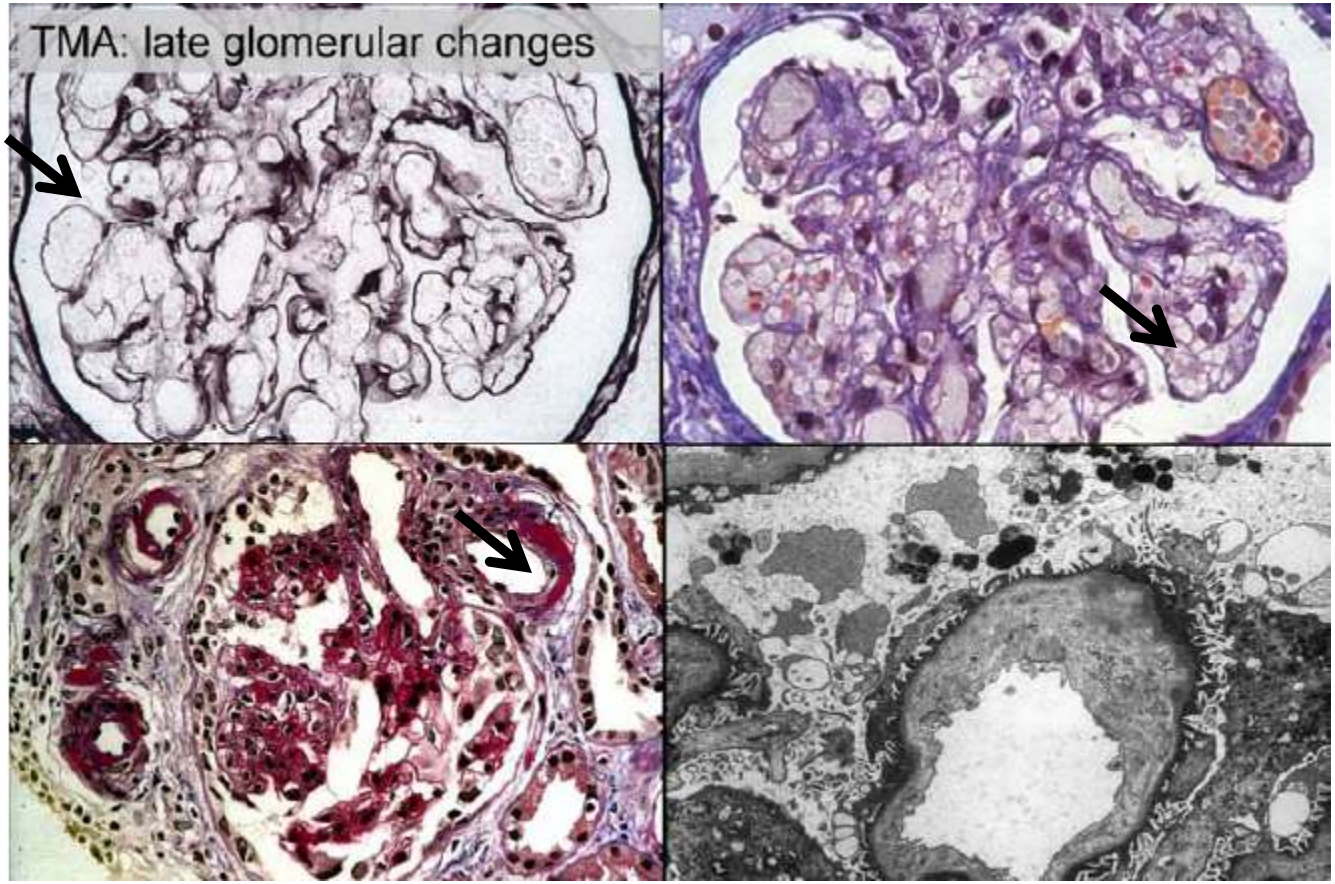
- TMA are microvascular occlusive disorders that represent a common pathway of different pathological processes

- Such disorders are characterized by endothelial injury, systemic or intrarenal aggregation of platelets and/or fibrin, mechanical injury to red blood cells, and thrombocytopenia

Early TMA : Glomerular lesions are characterized by endothelial cell injury, thrombus formation
Marked arteriolar intimal edema and severe stenosis

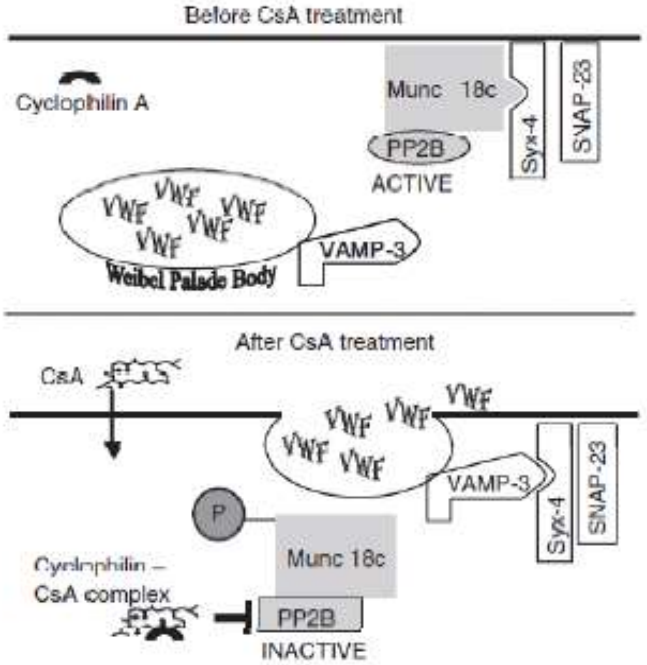


Late TMA: Glomerular capillary tufts show marked GBM duplication



Mechanisms of TMA

- Deficiency of ADAMTS-13
  - "Idiopathic" TTP
  - Ticlopidine/clopidogrel
- Increased production or retention of large vWF multimers
  - HUS
  - Cyclosporine/Tacrolimus
  - Systemic Inflammation

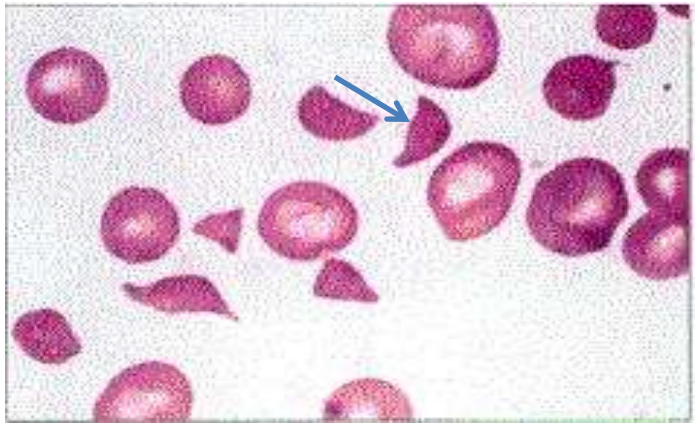


J Thromb Haemost. 2009 Jun;7(6):1009-18.

Thrombotic Thrombocytopenia Purpura

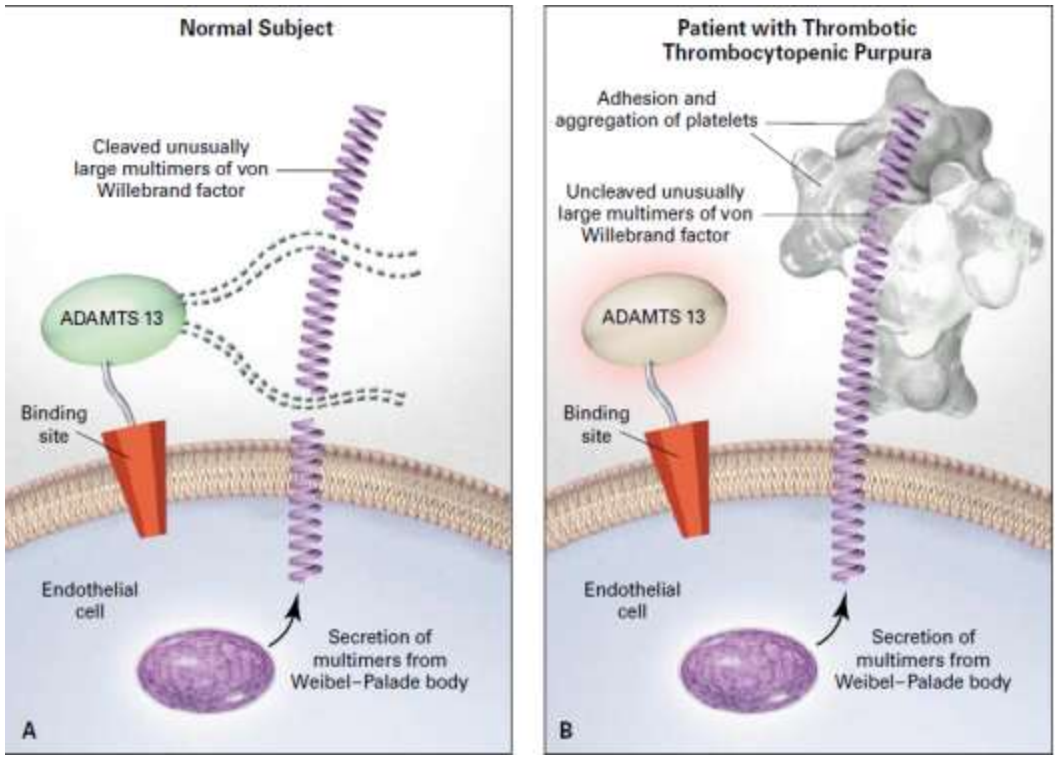
- Fever
- Thrombocytopenia
- Neurological abnormalities
- Microangiopathic hemolytic anemia
- Renal dysfunction

Increased LDH
Blood film
Raised reticulocyte count
Low haptoglobin
Negative Direst coombs test
ADAMTS13 assay



ADAMTS13

- Is responsible for cleavage of extra large multimers of vWF
- Congenital or acquired lack of ADAMTS13 has been linked to the development of TTP
- ADAMTS13 enzyme activity below 5 % is specific for symptomatic TTP



TTP

- Four general types exist:

  -congenital
  -idiopathic
  -drug induced
  -systemic disease

Congenital TTP

- May appear in early childhood

- Late onset TTP (triggered by infection, pregnancy)
-
- Caused by a deficiency of ADAMST13 (<5%)

- Treated with plasma transfusion

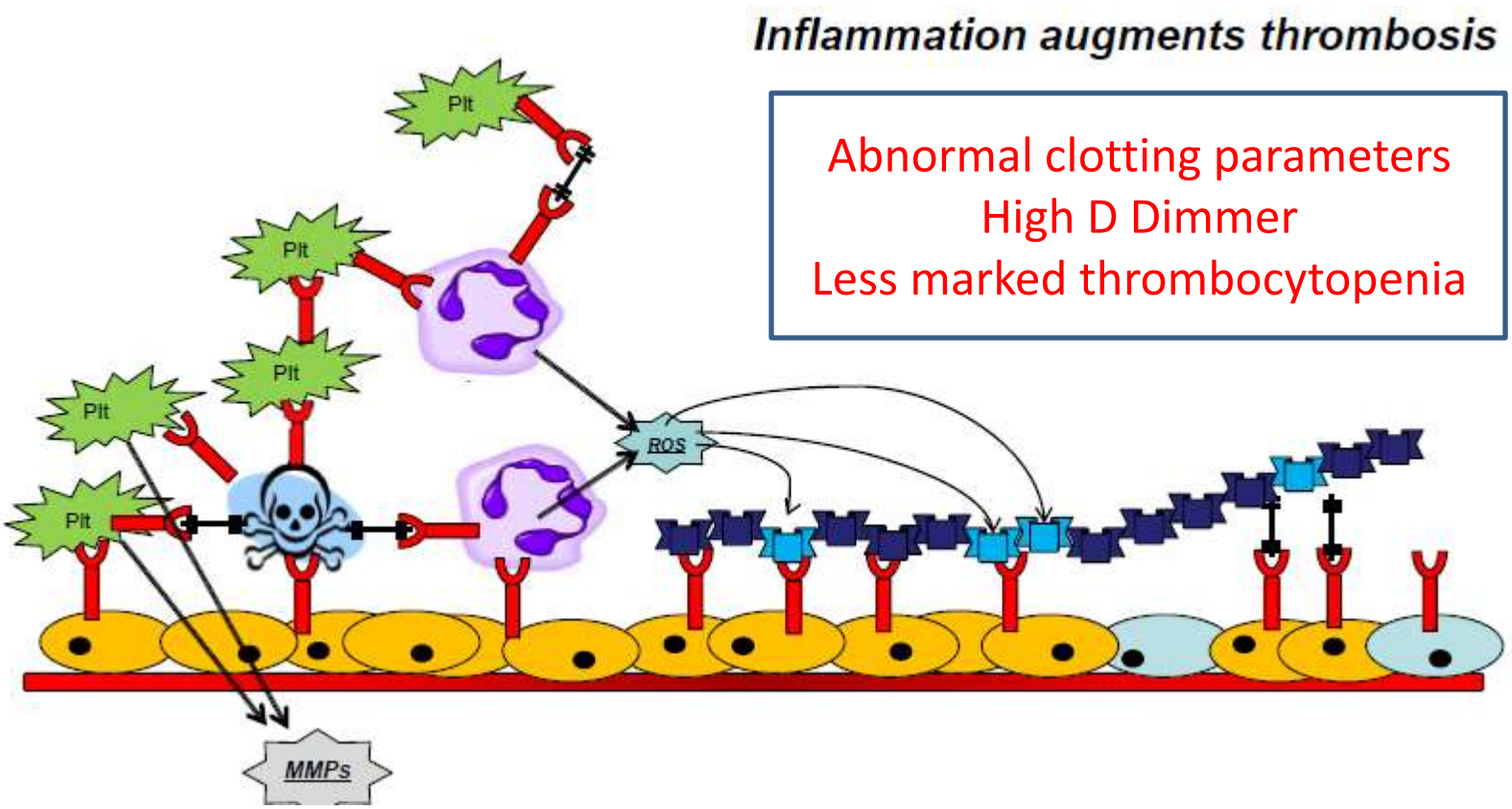
Drug-Induced TTP

- Quinine typically most common
- Anti-platelet agents ticlopidine and clopidogrel have been associated with TTP
- Calcinurin inhibitors

Systemic Disease Associated with TTP

- Antiphospholipid Antibody Syndrome
- Systemic Lupus Erythematosus
- Vascuilitis
- Malignant hypertension
- Malignancy

Disseminated Intravscular Coagulation (DIC)



Abnormal clotting parameters
High D Dimmer
Less marked thrombocytopenia

Pregnancy associated TMA

- Pregnancy associated TMA can be confused with other conditions such as preeclampsia, HELLP syndrome, sepsis, pregnancy associated fatty liver changes
- ADAMTS 13 deficiency (congenital or acquired) is the main cause of Pregnancy induced TMA
- Atypical HUS due to complement dysregulation was reported
- Plasma Exchange has increased survival from 10% to >80% and should starts on suspicion of TMA

Idiopathic TTP

- The most common form of TTP
- Thought to be caused by an autoantibody to ADAMST13

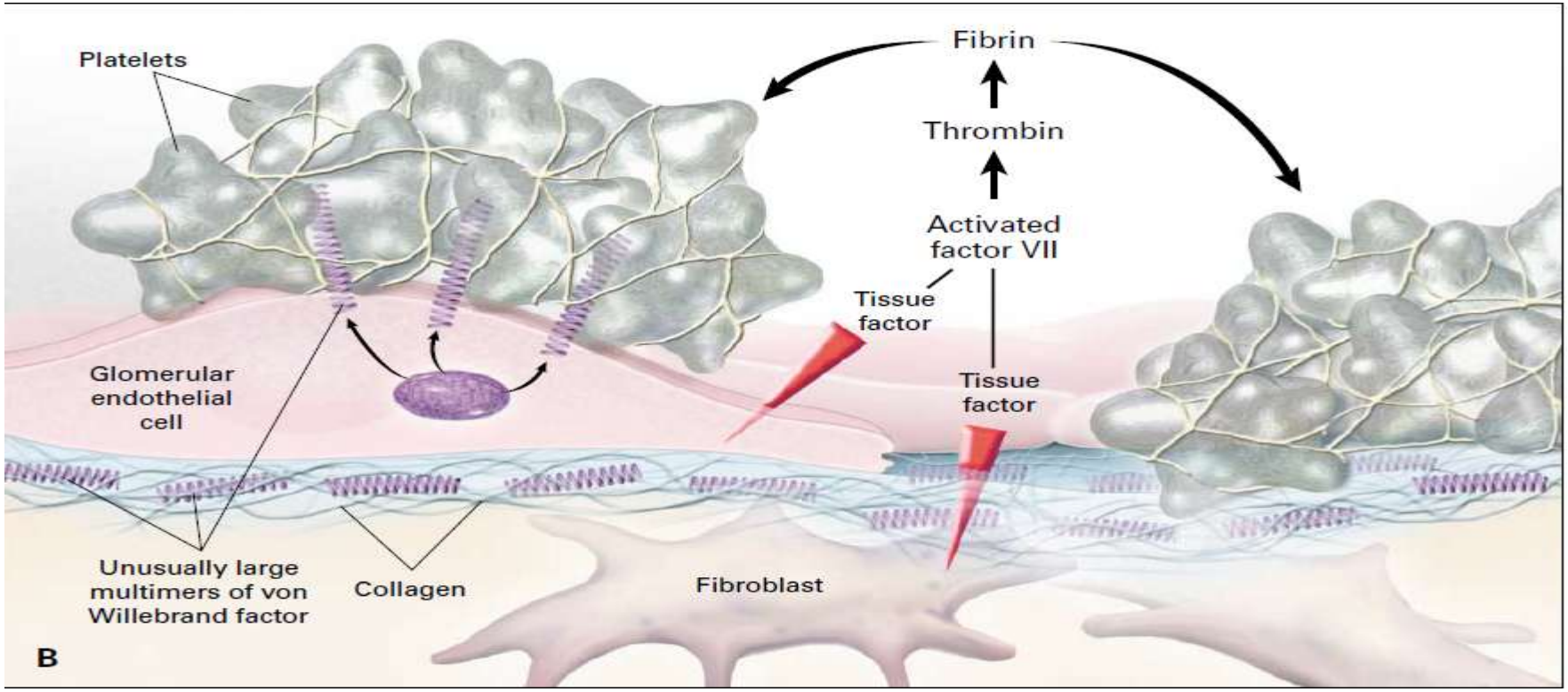
Hemolytic Uremic Syndrome

- Thrombocytopenia
- Renal dysfunction
- Microangiopathic hemolytic anemia

Post-Infectious HUS

- Organisms most commonly associated- E. Coli 0157:H7, shigella dysenteria

Shiga toxin binds to glycolipid. Exposure to Stx damages the endothelium resulting in the release of tissue factor and exposure of the platelets to **extra large von Willebrand factor multimers**



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German Outbreak of *Escherichia coli* O104:H4 Associated with Sprouts

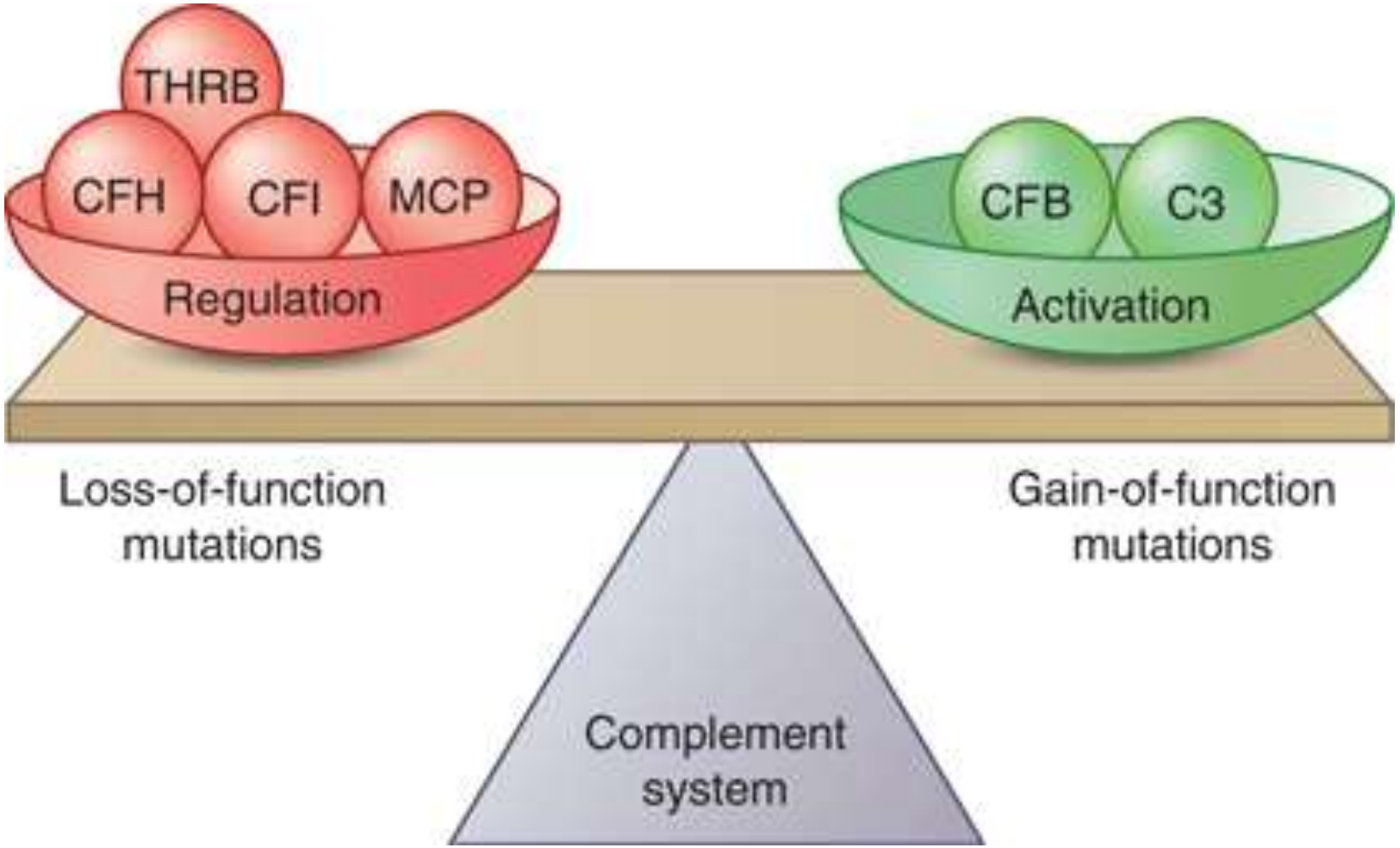
The outbreak affected mostly (87%)
individuals above the age of 20 years
2/3 were females
Poor outcome with high mortality

Post-Infectious HUS- Strep. Pneumonia

- Streptococcus pneumonia release neuraminidase resulting in exposure of T antigen on red cell surface
- IgM autoantibodies bind to T antigen resulting in hemolysis, thrombocytopenia and microthrombi
- Plasma exchange with 5% albumin may be helpful to remove antibodies against the T antigen (ASFA category III grade 2C)

Atypical familial HUS

Alternate Pathway regulators



Atypical HUS

- Factor H (CFH)
- Membrane-cofactor protein (MCP)
- Factor I (CFI)

Low C3 level suggests aHUS

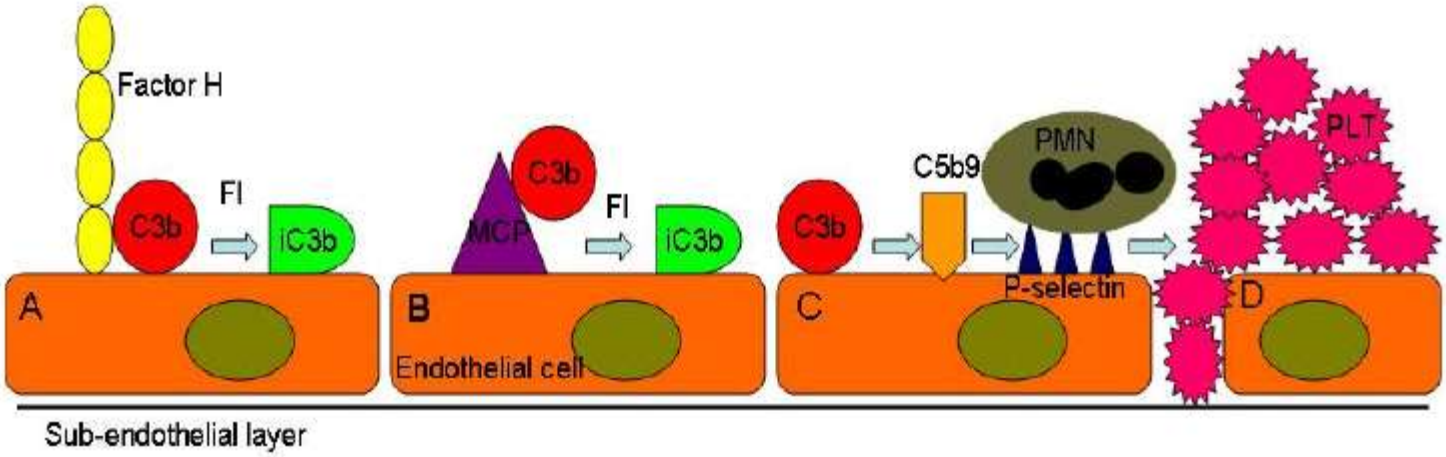


Figure 2. Proposed model for protective mechanism of factor H and membrane co-factor protein (MCP) against complement activation (A,B) in their deficiency membrane bound C3b is not effectively inactive (iC3b), followed by formation of membrane attack complex C5b9, leading to expression of adhesive molecules (p-selection) that favors leukocyte attachment (C), endothelial damage and finally platelet (PLT) adhesion and aggregation (D).

Complement and Atypical HUS

Protein	Gene	Source	Location	% of aHUS
Factor H	*CFH*	Liver	circulates	~ 15-30%
Factor I	*CFI*	Liver	circulates	~ 5-10%
Membrane Cofactor Protein	*MCP*	Widespread	Membrane bound	~ 10-15%
Factor B	*CFB*	Liver, ?	circulates	<5%
C3	*C3*	Liver, ?	circulates	~ 5-10%
Anti-FH-Ab	*CFHR1/ CFHR3*	Lymphocyte	circulates	~ 10%
Unknown				~ 40-50%

Inherited HUS- Factor H deficiency

- Factor H is an important enzyme in the complement cascade, which when absent, allows unregulated complement mediated cell lysis

- Such cell lysis is preferentially localized to glomerular endothelial cells causing the symptom complex of HUS

- Environmental triggers like viruses, bacteria, drugs, systemic disease, pregnancy causes sustained complement activation and endothelial damage

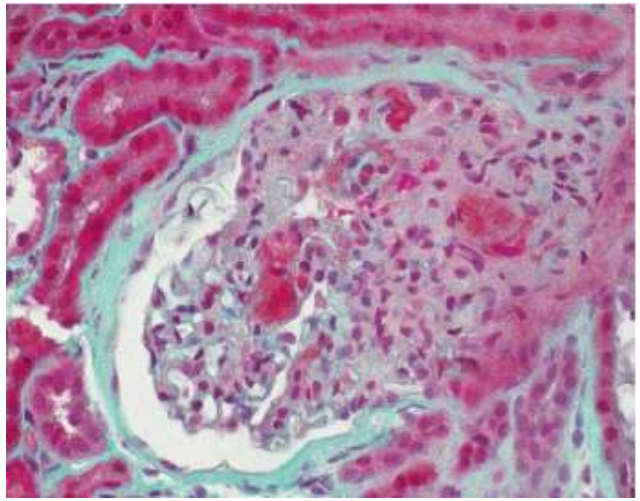
TMA after Renal Transplantation

De novo TMA post renal Transplant

- Calcineurin inhibitors (CNIs)
- Sirolimus
- Anticardiolipin antibodies
- Chronic hepatitis C virus infection
- CMV

Calcineurin inhibitors

- CNIs are associated with direct endothelial toxicity and vasoconstriction
- CNI have prothrombotic and antifibrinolytic actions
- Renal limited, can develop within days to few weeks and present as DGF
- Severe forms are associated with systemic TMA



Usually respond to dose reduction or discontinuation of CNI± PE

Acute antibody mediated rejection (AMR)

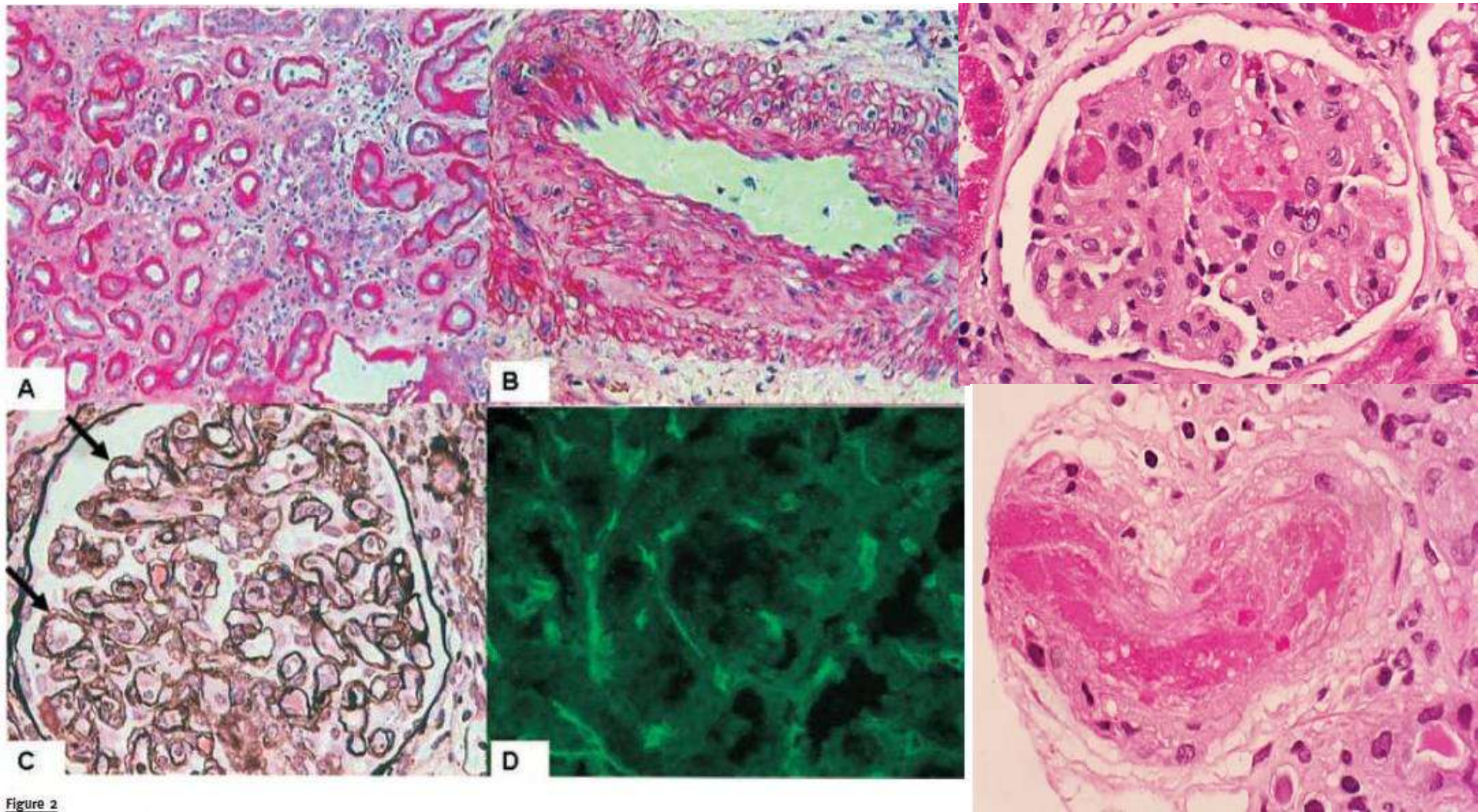


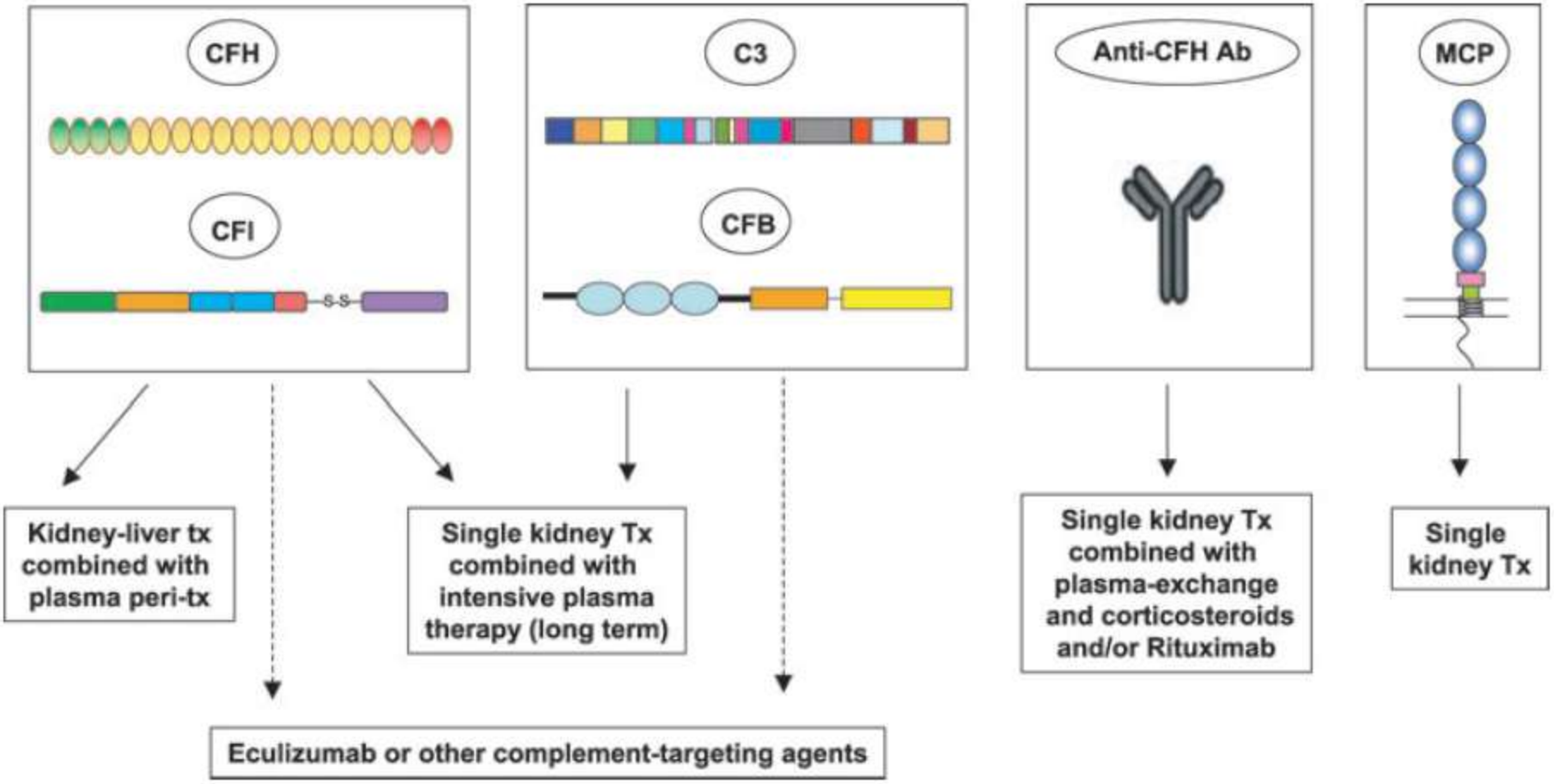
Figure 2

Recurrent post transplant TMA

- The highest rate of Recurrent TMA is seen in aHUS secondary to complement dysregulation (30-100%), the highest with gene mutations

- Living related RTx is contraindicated in aHUS as nephrectomy my predispose to TMA in living related donor with genetic susceptibility

Noris and Remuzzi



Treatment Options: Plasma exchange or not?

Therapy of TTP/HUS: Plasma Exchange

- Plasma exchange has become standard of care for all patients given the diagnosis of TTP
- Prior to plasma exchange, the 6 month mortality of patients with TTP was greater than 90%
- Goal is to rapidly reduce circulating levels of autoantibody against ADAMST13 and other possible prothrombotic compounds present in patients' serum
- The recommended TPE replacement fluid is plasma or plasma with cryoprecipitate removed (i.e. the plasma portion that is depleted with ultra-large VWF and large plasma VWF)

Table 1. ASFA categories

Category	Definition
I	Apheresis, alone or in conjunction with other therapies, is considered a first-line intervention for these indications.
II	Apheresis, alone or in conjunction with other therapies, is considered a second-line intervention for these indications.
III	Role of apheresis therapy has not been established for these indications. Decisions should be made on case-by-case basis.
IV	Apheresis therapy is ineffective or harmful. IRB approval should be sought if apheresis is performed for these indications.

Table 2. Grading recommendations for ASFA guidelines

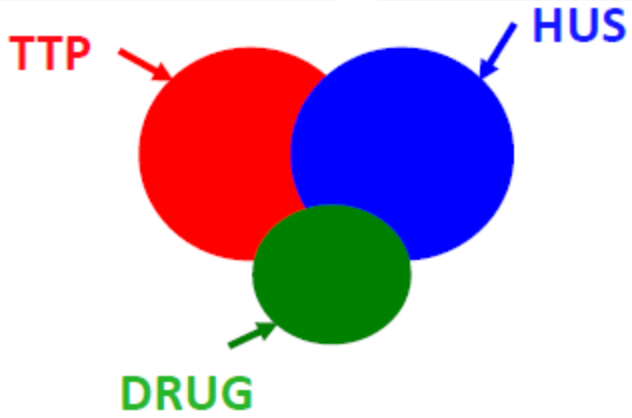
GRADE	Definition
1A	Strong recommendation with high-quality evidence. Apheresis can be utilized without reservation.
1B	Strong recommendation with moderate-quality evidence. Apheresis can be utilized without reservation.
1C	Strong recommendation with low-quality evidence. Apheresis recommendation may change with additional evidence.
2A	Weak recommendation with high-quality evidence. Apheresis may be considered based on individual circumstance.
2B	Weak recommendation with moderate-quality evidence. Apheresis may be considered based on individual circumstance.
2C	Weak recommendation with low-quality evidence. Alternative therapies may be equally effective.

Therapeutic plasma exchange is/may be indicated		
TTP	I	1A
HUS		
Associated with *Streptococcus pneumonia*	III	2C
Atypical HUS		
Factor H antibodies	I	2C
Complement gene mutations	II	2C
Drug-associated TMA		
Ticlopidine	I	2B
Clopidogrel	III	1B
Cyclosporine/tacrolimus	III	2C
Transplantation-associated TMA	III	2C
Therapeutic plasma exchange is NOT indicated		
HUS		
Associated with shiga toxin-producing *Escherichia coli*	IV	1C
Atypical HUS		
Membrane cofactor protein mutations	IV	1C
Drug-associated TMA		
Gemcitabine	IV	2C
Quinine	IV	2C

Treatment plans…

Goal: Remove inhibitor & replace enzyme
Replacement: FFP / albumin
Frequency: Daily
End point: Normalize platelet count

Goal: dHUS → don't do
aHUS → replace factor H
Replacement: FFP
Frequency: Longest tolerable interval
End point: Prevent / treat renal failure



Goal: Remove inhibitor & replace enzyme (ticlopidine), autoimmunity (?), endothelial damage, drug dependent antibodies
Replacement: FFP / albumin
Frequency: Daily or every other day
End point: Normalize platelet count

Corticosteroid

Intravenous daily methylprednisolone (e.g. 1 g/d for three consecutive days – adult dose) or high dose oral prednisolone (e.g. 1 mg/kg/d) should be considered (1B).

Rituximab

Recommendation

1 In acute idiopathic TTP with neurological/cardiac pathology, which are associated with a high mortality, rituximab should be considered on admission, in conjunction with PEX and steroids (1B).
2 Patients with refractory or relapsing immune-mediated TTP should be offered rituximab (1B).

Eculizumab

- Anti-C5 monoclonal antibody
- Prevent generation of membrane attack complex
- Recently approved in the USA and Europe as **first line treatment** for aHUS
- Maintenance therapy appears to be effective
- Patients older than 18 years of age 900 mg IV weekly for 4 weeks, then 1200 mg IV as the fifth dose, followed by 1200 mg IV biweekly

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doi: 10.1093/ndt/gfn687
Advance Access publication 18 December 2008

Preliminary Communication

NDT
Nephrology Dialysis Transplantation

Athrombocytopenic thrombotic microangiopathy, a condition that could be overlooked based on current diagnostic criteria

Sacha A. De Serres and Paul Isenring

The Nephrology Research Group, L'Hôtel-Dieu de Québec Research Institution, Department of Medicine, Faculty of Medicine, Laval University, Québec, Canada

Thrombocytopenia was found in only 56% but serum LDH was still elevated in most (mean 619 U/L)

higher percentage of athrombocytopenic subjects who required dialysis

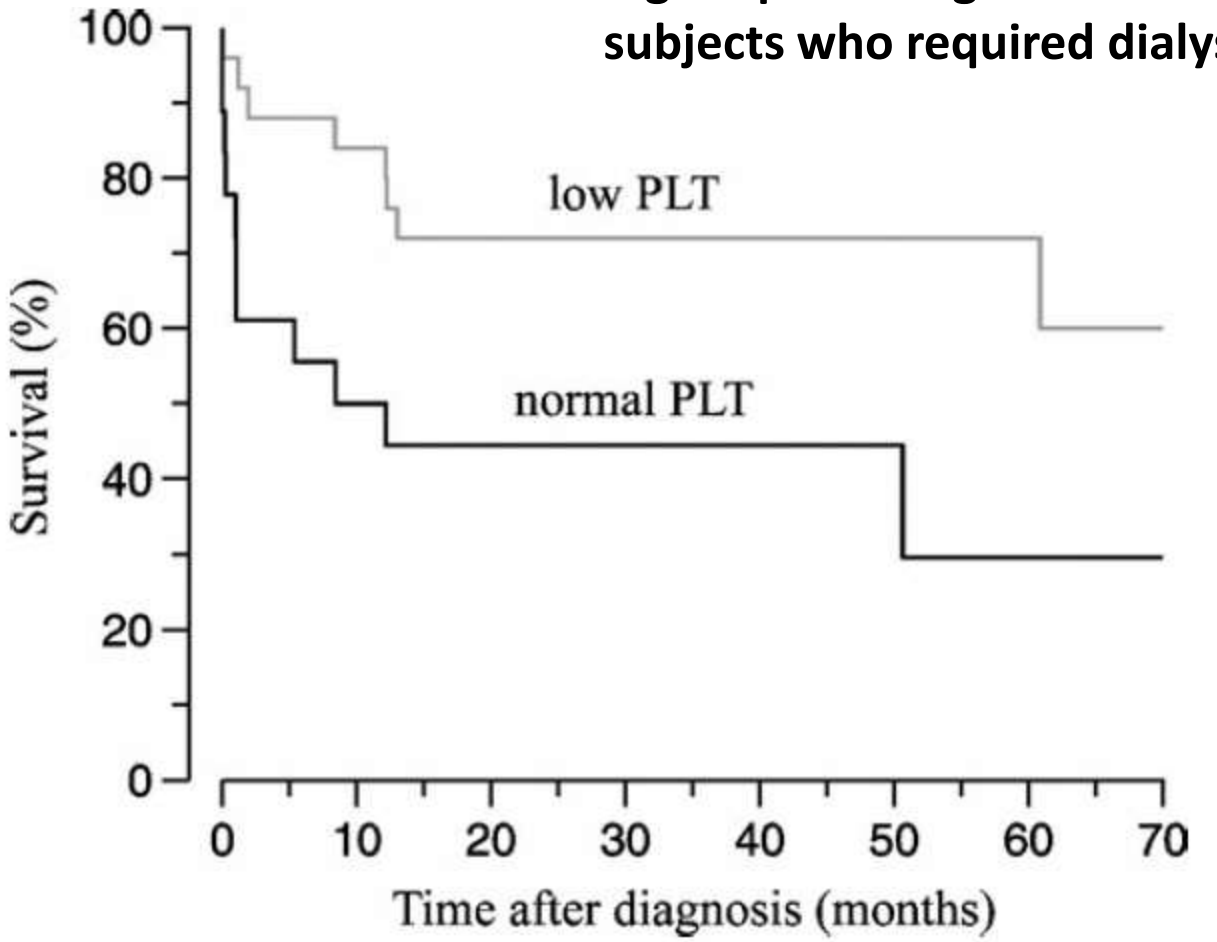
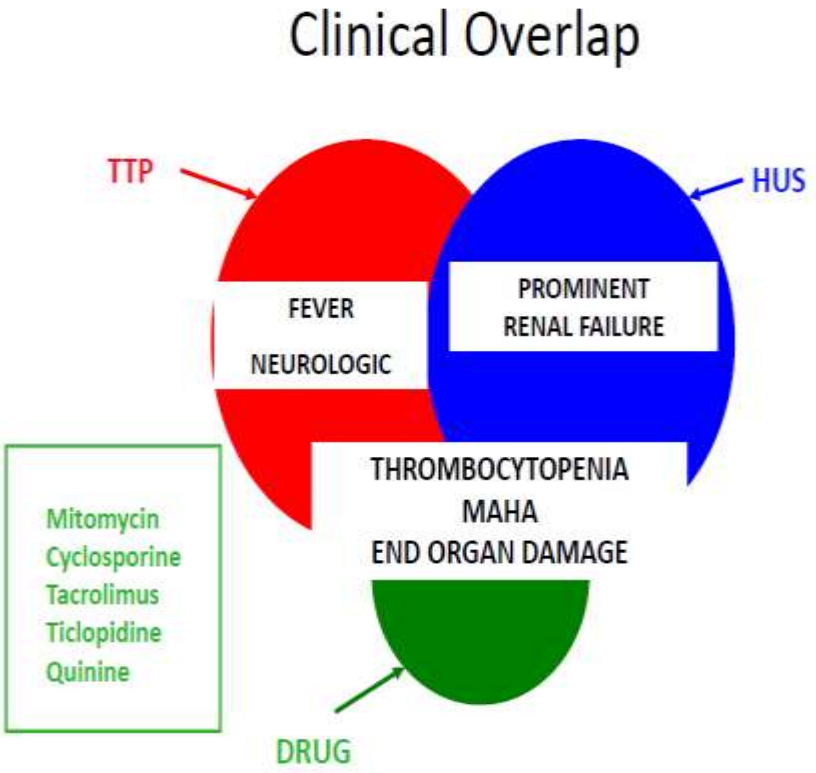


Fig. 1. Patient survival following histological diagnosis of TMA. Based on a Kaplan–Meier analysis, curves were significantly different statistically between the 'low PLT' and 'normal PLT' groups ($P = 0.023$).

Conclusions

- HUS and TTP constitute a single entity acting through endothelial damage

- Plasma therapy has reduced mortality and should be instituted on clinical suspicion of TTP/HUS preferably within **4-8 hours**



Conclusions

- Rituximab 4 doses 375 mg/ week has been used in refractory and relapsing TTP
- Long term Ecluzimab has been approved as first line therapy in a HUS
- aHUS has high recurrence rate after renal transplantation and living related transplantation is contraindicated


Thank You